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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/987,687	11/15/2001	Matthew C. Coffey	032775-078	7186

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	14

DATE MAILED: 07/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/987,687	COFFEY ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 5/20/03, as Paper No. 15. The amendment has been entered. Claims 1, and 8-14 have been amended. Claims 1-21 are currently pending in the application and are examined herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Rejections - 35 USC § 102

1. Claims 1, 7 and 10-13 remain rejected under 35 U.S.C. 102(b) as being anticipated by Kooby et al. (FASEB Journal, Aug. 1999; 13:1325-1334) for the reasons of record.

Response to Arguments

2. Applicant's arguments filed 5/20/03 have been fully considered but they are not persuasive. Applicants disagree with the Examiner's interpretation of the claim as encompassing a single injection of a large volume of a viral composition to deliver the virus to "multiple sites within the tumor". The Applicants point to the specification (p. 14, lines 5-10) which indicates two alternative methods of delivering the viral composition to the tumor one where the tumor is injected multiple times and alternatively where the virus is delivered by injected to a single site in a large volume which enables a wide spread of the virus (See p. 6 of the response filed 5/20/03). The Applicants argue, "There is no indication that multiple injections can be interpreted as a single injection of a large volume." (See p. 7 lines 2-3). Applicants argue that if

multiple is defined in the specification, then it should be interpreted as "two or more" based on the plain meaning of multiple, as evidenced by The American Heritage Dictionary. Based on these arguments Applicants assert that delivery to multiple sites (required in the claimed invention) can not be interpreted as a single injection; and Kooby does not teach every element of the claim because it does not teach delivering the viral composition to multiple sites within the tumor.

3. In response, it is respectfully pointed out that the claims do not explicitly indicate that multiple injections are required. The claims only specifically indicate "delivering on the same day a composition comprising the virus to multiple sites inside the solid tumor". The Examiner makes a distinction between "multiple injections" and "multiple sites". The term "multiple sites" does not necessarily require multiple injections. "Multiple sites" only requires the delivery to multiple places within the tumor, such as to different cells within the tumor. As indicated by the Applicants in the response, p. 14 lines 5-10 of the specification indicates that two alternative methods of delivering the viral composition to a tumor including injecting to a single site in a large volume **which enables a wide spread of the virus.** (Emphasis added). Therefore, the interpretation that a single injection of a large volume could deliver the virus composition to "multiple sites" within the solid tumor is accurate because injecting a single site with a large volume "enables a wide spread of the virus"—"a wide spread of the virus" being indicative of delivery to multiple sites within the tumor. Furthermore, as indicated in the footnote of p. 7 of the response, the specification also teaches that the two alternative methods described can be combined.

Furthermore, it appears when the Applicants make the argument, "There is no indication

that multiple injections can be interpreted as a single injection of a large volume." (See p. 7 lines 2-3), that the Applicants are arguing limitations not present in the claims because the claims do not explicitly indicate that multiple injections are performed, only that the virus is delivered to multiple sites within the tumor. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Therefore, Kooby does meet all of the limitations of the instant claims including delivery of the virus to multiple sites within the tumor, and the rejection is not withdrawn.

Claim Rejections - 35 USC § 103

1. Claims 1-6 and 14-21 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kooby et al. (FASEB Journal, Aug. 1999; 13:1325-1334) in view of Lee et al. (WO 99/08692) for the reasons of record and the reasons set forth below.

It is acknowledged that claim 14 has been amended such that the claim now encompasses an additional step wherein the additional step comprises topical administration of the viral composition to the tumor. However, this limitation is also obvious over the teachings of Kooby and Lee as indicated below. It is noted that the amendment to claim 14 changed the scope of claim 14 and claims 15-21 which depend on claim 14.

Kooby teaches a method for delivering a virus to a solid tumor to reduce growth of the tumor, comprising administering an effective amount of virus to a subject bearing the tumor, wherein the virus is capable of selectively replicating in and killing tumor cells, by a base administration selected from the group consisting of:

(a) delivering a composition comprising the virus to multiple sites inside the tumor; and

(b) delivering directly into the tumor a composition comprising the virus, wherein the volume of the viral composition is between about 10% and 100% of the volume of the tumor, as indicated in the rejection of claim 1 above.

Kooby does not teach that the virus can be a reovirus, a mammalian reovirus, a human reovirus, a serotype 3 human reovirus, or a Dearing strain serotype 3 human reovirus or that the method of delivery further comprises at least one additional administration comprising delivering the composition by topical administration (see claim 14).

Lee teaches a method for delivering a reovirus serotype 3 Daring strain virus to a solid tumor to reduce growth of the tumor, comprising administering an effective amount of virus to a subject bearing the tumor, wherein the virus is capable of selectively replicating in and killing tumor cells, wherein the oncolytic viral composition can be administered by injection directly into the neoplasm (see p. 8, lines 21-22), as well as topically (e.g., melanomas) (see p. 9, line 4). Lee also teaches that the viral composition(s) can be administered in a single dose or in multiple doses (i.e. more than one dose) and the multiple doses can be administered concurrently (at the same time) or consecutively (i.e. either before or after the base administration). (See, for instance, abstract; p.3 lines 1-15; p.9, lines 17-20; p.34, lines 9-17; Examples 9 and 10; and Claim 38). Lee also teaches that the reovirus is not known to be associated with disease (see p. 3, lines 15-18), thus making it a safer therapeutic virus than viruses that are known to cause diseases.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by Kooby such that the viral vector

that is delivered into the tumor is a Dearing strain serotype 3 virus, and to further modify the method of Kooby such that the method also comprised an additional administration of the viral composition by topical administration to the tumors (wherein the tumor is a melanoma), with a reasonable expectation of success.

One of ordinary skill would have been motivated to substitute the modified HSV-1 virus of Kooby with the Dearing strain 3 reovirus of Lee in order to increase the safety of the method as herpes viruses are known to causes diseases in subjects while reovirus is not known to be associated with any disease. Furthermore, one of ordinary skill would have been motivated to modify the method of Kooby such that the method further comprises an additional administration of the viral composition to the tumor by topical administration of the composition to the tumor wherein the tumor is a melanoma because Lee teaches that effective treatment depends on several factors including the amount of virus administered, the type and size of the tumors and indicates that multiple administrations may be required (see p. 9, lines 7-20), wherein the administrations can be by direct injection and topical administration and administered concurrently or consecutively.

Response to Arguments

2. Applicant's arguments filed 5/20/03 have been fully considered but they are not persuasive.

3. Applicants argue that Kooby does not teach delivery to multiple sites within the tumor on the same day wherein the volume of the composition delivered is between 10% and 100% of the volume of the tumor. Applicants also argue that Lee does not teach delivery to multiple sites on

the same day or delivery of between 10% and 100% of the volume of the tumor. The Applicants contend that the references do not teach all of the limitations of the claims, nor do the references provide motivation to combine the reference, and the rejections should therefore be withdrawn (see p. 7-8 of the response).

4. In response, as indicated above Kooby does teach the delivery to "multiple sites" within the tumor because Kooby teaches an injection of a large volume (i.e. ~100% of the volume of the tumor) into the tumor which would spread to multiple sites within the tumor on the same day. Furthermore, as indicated in the previous Office Action, Kooby teaches administration of 50ul of the viral composition to tumors that are ~50mm^3. It is noted that ~50mm^3= ~0.050ml= ~50µl. Therefore, injecting 50µl constitutes injecting about 100% of the volume of the tumor, thus Kooby teaches injection of about 100% of the volume of the tumor.

5. Regarding the teachings of Lee, as indicated in the previous Office Action, Lee teaches methods of delivering a Dearing strain virus (which meets the limitation of claims 2-6) to a tumor by injecting a Dearing strain viral composition into the tumor multiple times and indicates that the administrations can be concurrent or consecutive. Furthermore, as previously mentioned Lee indicates that effective treatment depends on several factors including the amount of virus administered, the type and size of the tumors and indicates that multiple doses may be required, thus indicating that the administrations, including volume and number of injections, would be a matter of routine optimization to the ordinary artisan.

6. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching,

suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, as mentioned in the prior Office Action it would have been obvious to one of ordinary skill in the art to modify the method of Kooby such that the method constituted delivering the Dearing strain virus in place of the modified HSV virus taught by Kooby. It is noted that the Dearing strain virus and the modified HSV virus used by Kooby were both known oncolytic virus useful for anticancer therapy. Furthermore, as previously set forth, the motivation to substitute the modified HSV-1 virus of Kooby with the Dearing strain 3 reovirus of Lee in order to increase the safety of the method as herpes viruses are known to causes diseases in subjects while reovirus is not known to be associated with any disease. Furthermore, one of ordinary skill would have been motivated to modify the method of Kooby such that the method further comprises an additional administration of the virus composition to the tumor wherein the composition is either administered to multiple sites inside the tumor (either concurrently or before or after the base administration) or another injection of the composition comprising a volume between about 10% to about 100% of the volume of the tumor is administered to the tumor in order to sufficiently treat the tumor because Lee indicates that effective treatment depends on several factors including the amount of virus administered, the type and size of the tumors and indicates that multiple doses may be required.

Therefore, the rejection of claims 1-6 and 14-21 are not withdrawn.

7. Claims 1, 8 and 9 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kooby et al. (FASEB Journal, Aug. 1999; 13:1325-1334) in view Barber et al. (US Patent 5,662,896) for the reasons of record.

Response to Arguments

8. Applicant's arguments filed 5/20/03 have been fully considered but they are not persuasive.

9. Applicants argue that although Barber teaches multiple injections of an anti-tumor vector composition to a tumor, Barber does not teach multiple injections on the same day. Applicants also contend that Barber teaches away from claimed invention because Barber teaches to administer 25-fold to 200-fold volume of composition to the tumor, which is outside the claimed range of 10%-100% of the tumor volume. Finally, Applicants argue that there is no suggestion or motivation to combine the references.

10. In response, the examiner disagrees with the Applicants argument that Barber does not teach multiple injections on the same day. As mentioned in the previous Office Action, Barber teaches "multiple injections of the vector are given to the tumor every two to three days" (see Barber, column 37, lines 44-45). Therefore Barber does teach giving multiple injections on the same day followed by multiple injections two to three days later.

11. Regarding the argument that Barber teaches away from the claimed invention, it is noted that Kooby teaches the administration of 10%-100% of the volume of the tumor. Therefore, it appears that the Applicants are arguing the references individually. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re*

Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

12. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Barber teaches that administering a anti-tumor vector composition to a tumor by injecting the composition into the tumor at multiple sites on the same is the most effective treatment. Therefore, one of skill in the art would have been motivated to modify the method of Kooby to encompass multiple injections (thus delivering the virus to at least 5 sites within the tumor) in order to the make the most effective treatment.

Conclusion

No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Anne-marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER

J. Eric Angell
July 26, 2003